

- having molecular weights between 2,000 and 8,000,

- soluble in an aqueous-alcoholic medium (water-ethanol) having a titer of 55-61° GL,

- tending to insolubility in a water-ethanol medium having a higher alcohol content,

- insoluble in pure alcohol, and having a Yin-Wessler titer and a USP titer respectively in a ratio of at least 3.

30. Mucopolysaccharides according to claim 29, having Yin/Wessler ratios higher than 6.

31. Mucopolysaccharides according to claim 29, having YIN-WESSLER/USP ratios higher than 10 even 16.

B
32. Mucopolysaccharides according to claim 29 wherein said constituents, in a gel-filtration operation on a column of gel of polyacrylamide and of agarose, in a bead form of the type marketed under the name ULTROGEL AcA 44, are obtained in the 1.5 litres of eluate which follow the elution of a volume of 2.5 litres, dead volume not included, when the gel-filtration is conducted, at a flow rate of 200 ml/hour, on a column having a diameter of 1000 mm and a height of 1 m and when the concentration a mucopolysaccharide and the volume of the solution placed on the column have been respectively 50 mg/ml and 37.5 ml.

33. Mucopolysaccharides according to claim 29, claim 1, wherein said constituents, in a gel-permeation system on

columns filled with silica with a granulometry of 10 to 100 microns, of 250 mm height and 9 mm diameter, have a retention time of the order of 5.7 to 7.5, notably from 6.7 to 7.0 minutes in such column, when 50 ul of a solution of 1.3 mg/ml of this fraction in a 0.02 M Na₂SO₄ buffer, are placed on this column and then eluted at a flow rate of 3 ml/minute.

34. Mucopolysaccharides according to claim 29 having YIN-WESSLER titers of at least about 3.55 with a YIN-WESSLER titer of at least about 160 u/mg.

35. Mucopolysaccharides according to claim 29 having YIN-WESSLER titers higher than 130.

B
36. Mucopolysaccharides according to claim 29 comprising constituents capable of being fixed on Antithrombin III (or AT III).

37. Mucopolysaccharides according to claim 29 comprising constituents capable of being fixed on an AT III fixed to a support, such as agarose, in an 0.2 M NaCL; 0.05 M tris-HCL buffer at ph 7.5 and by YIN-Wessler and USP titers which are in a ration (YW/USP ratio) at least equal to 6, the Yin-Wessler titer itself being at least equal to 300 u/mg.

38. Mucopolysaccharides according to claim 37 having YW/USP ratio higher than 18 and a Yin-Wessler activity higher than 900 U/mg.

39. Mucopolysaccharides according to claim 37 having a YW/USP ration higher than 50.

40. Mucopolysaccharides according to claim 37 having a YW/USP ration higher than 65 with a YIN-WESSLER activity higher than 1 300 U/mg.

B1

41. Mucopolysaccharides according to claim 29 having an NMR spectrum for the (¹H) proton, effected on a solution of this compound dissolved in deuteriated water at 35°C with a radiation of 270 megahertz, which comprises, as characteristic elements of the spectrum, resonance signals which, for chemical displacements of the order of 4,8 and 5.2 ppm, are substantially weaker than the resonance signal which is also observed for a chemical displacement of the order of 5.4 ppm (reference for the measurement of the displacements : sodium 3-trimethylsilyl propionate 2.2 3.3-d₄).

42. Mucopolysaccharides according to claim 29 characterized by an NMR spectrum for carbon 13 (¹³C), carried out on a solution of this compound dissolved in deuteriated water with a radiation of 20 MHz, which comprises, as characteristic elements of the spectrum (reference for the measurement of the displacements : tetramethylsilane) :

-the practical absence of resonance signals characteristic of the presence of OH groups on the primary carbon (in the 6 position) of the glucosamine units contained in said mucopolysaccharide fraction,

-supplementary signals, in the region of the (I₁) and (G₁) signals, in region corresponding to the

chemical displacements of the order of 100 ppm,
-a supplementary signal (G_2) close to the
N-sulphated G_2 signal in the 60 ppm region
-the presence of a resonance signal in the 75 ppm
region.

43. Mucopolysaccharides according to claim 32 having a NMR spectrum in conformity with that of Figure 13

44. Mucopolysaccharides according to claim 33 having a NMR spectrum in conformity with that of Figure 14.

B' 45. Mucopolysaccharides according to claim 34 having a NMR spectrum in conformity with that of Figure 15.

46. Mucopolysaccharides according to claim 29 comprising constituents having glucosamine units with all the primary positions sulphated and including one N-acetylglucosamine unit per two units of 2-O-sulphate iduronic acid and per two N-sulphate-glucosamine units, said constituents being fixable on AT III and acting selectively on the inhibition of the Xa factor in vitro and in vivo.

47. Mucopolysaccharides according to claim 29 comprising consisting of an homogeneous oligosaccharide :

-fixable on AT III having an NMR spectrum for the (1H) proton, effected on a solution of this compound dissolved in deuteriated water at 35°C with a radiation of 270 megahertz, which comprises, as characteristic elements of the

spectrum, resonance signals which, for chemical displacements of the order of 4.8 and 5.2 ppm, are substantially weaker than the resonance signal which is also observed for a chemical displacement of the order of 5.4 ppm (reference for the measurement of the displacements : sodium 3-trimethylsilyl propionate 2.2, 3.3-d₄) and an NMR spectrum for carbon 13(¹³C), carried out on a solution of this compound dissolved in deuteriated water with a radiation of 20 MHz, which comprises, as characteristic elements of the spectrum (reference for the measurement of the displacements : tetramethylsilane) :

B' the practical absence of resonance signals characteristic of the presence of OH groups on the primary carbon (in the 6 position) of the glucosamine units contained in said mucopolysaccharides.

-supplementary signals, in the region of the (I₁) and (G₁) signals, in regions corresponding to the chemical displacement of the order of 100 ppm,

-a supplementary signal (G_x) close to the N-sulphated G₂ signal in the 60 ppm region,

-the presence of resonance signal in the 75 ppm region, and further comprising from 8 to 12, notably 10 monosaccharide units, wherein all the primary position of the glucosamine units are sulphated;

-this oligosaccharide including one N-acetyl-glucosamine unit per two units of 2-O-sulphate iduronic acid and per two N-sulphate-glucosamine units, the other saccharides being of a different nature and including distinct substituents.

B1

48. Fraction of mucopolysaccharides or compound formed by a homogeneous oligosaccharide

-comprising from 8 to 12, notably 10 monosaccharide units ;

-all the primary position of the glucosamine units of this oligosaccharide being sulphated;

-this oligosaccharide including one N-acetyl-glucosamine unit per two units of 2-O-sulphate iduronic acid and per two N-sulphate-glucosamine units, the other saccharides being of a different nature and including distinct substituents ;

-exerting selective inhibition of the Xa factor *in vitro* and *in vivo* ;

C

49. Fraction or compound according to claim 48 having an NMR spectrum for the (^1H) proton, effected on a solution of this compound dissolved in deuteriated water at 35°C with a radiation fo 270 megahertz, which comprises, as characteristic elements of the spectrum, resonance signals which, for chemical displacements of the order of 4,8 and 5.2 ppm, are substantially weaker than the resonance signal which is also observed for a chemical displacement of the order of 5.4 ppm (reference for the measurement of the displacements : sodium 3-trimethylsilyl propionate 2,2 3,3-d_r).

50. Fraction or compound according to claim 48 charaterized by an NMR spectrum for carbon 13 (^{13}C), carried

out on a solution of this compound dissolved in deuteriated water with a radiation of 20 MHz, which comprises, as characteristic elements of the spectrum (reference for the measurement of the displacements : (tetramethylsilane) :

-the practical absence of resonace signals characteristic of the presence of OH groups on the primary carbon (in the 6 position) of the glucosamine units contained in said mucopolysaccharide fraction,

-supplementary signals, in the region of the (I_1) and (G_1) signals, in regions corresponding to the chemical displacements of the order of 100 ppm,

- a supplementary signal (G_2) close to the N-sulphated G_2 signal in the 60 ppm region,

B/ C/ 51. Mucopolysaccharides according to claim 29 wherein said constituents are in the form of salts of at least one physiologically acceptable metal, such as sodium or calcium.

52. Mucopolysaccharides according to claim 29 wherein said constituents have a molecular weight of 4,000 to 8,000.

53. Mucopolysaccharides according to claim 29, wherein said constituents have a molecular weight from 4,000 to 8,000 and an NMR spectrum for ^{13}C , recorded with solution of said mucopolysaccharides indeuteriated water with a radiation of 20 MHz, with the following typical signals

23.4 ppm : CH_3 of NH-acetyl group

54.7 ppm : carbons in position 2 of the acetylated glucosamine moieties

R-126
B1

59.2 and 58.8 ppm : carbons in position 2 of the sulfate glucosamine moieties (splitting).

61.7 ppm : carbons in position 6 with -OH groups

67.4 ppm : carbons in position 6 with -O-sulfated groups

98.3** ppm : carbons in position 1

100.00 ppm **: carbons in position 1 of the sulfated iduronic acid units and

103 ppm : carbons in position 1 of the glucuronic acid units.

54

55. Mucopolysaccharides according to claim 29, wherein said constituents have a molecular weight of 4,000 to 8,000 a content in N-acetyl glucosamine and glucuronic acid moieties higher than heparin, a similar content in iduronic acid moieties and a sulphate content lower than heparin.

55-

56. Mucopolysaccharides according to claim 29, having an NMR spectrum in accordance with that of figure 1a.

56

57. The process of claim 58 for preparing a mucopolysaccharide fraction having a high Yin-Wessler titer and a low USP titer comprising :

-suspending in an aqueous-alcoholic medium of the water-ethanol type, having a titer comprised between about 55 and about 61°GL, a substance based on heparin or heparinic constituents whose molecular weights range from 2,000 to 50,000k tyis substance having a reduced content of inorganic salts, less than 1% by weight,

-separating the insoluble fraction and recovering the solution containing the dissolved mucopolysaccharide fraction, from which it can in its turn be separated notably by alcoholic precipitation.

⁵⁷ 58. Process according to claim ⁵⁷, comprising subjecting an aqueous solution of said MPS fraction to a gel-filtration and recovering the fractions having higher YIN-WESSLER/USP titer ratios.

⁵⁸ 59. Process for preparing a mucopolysaccharide fraction having a high YIN-WESSLER titer and a low USP titer comprising :

B/ -suspending in an aqueous-alcoholic medium of the water-ethanol type, having a titer comprised between about 55 and about 61 GL, a substance based on heparin or heparinic constituents whose molecular weights range from 2,000 to 50,000, this substance having a reduced content of inorganic salts, less than 1% by weight,

-separating the insoluble fraction and recovering the solution containing the dissolved mucopolysaccharide fraction, from which it can in its turn be separated, notably by alcoholic precipitation ;

-subjecting an aqueous solution of said MPS fraction to a gel-filtration and recovering the fractions having higher YIN-WESLLER/USP titer ratio and comprising producing further such enrichment.

-by contacting any of the preceding fractions with immobilized antithrobin III to produce selective

fixation thereon of the most active fractions in terms of YIN-WESSLER activity and recovering the latter by elution with a buffer capable of producing desorption.

⁵⁹
60. A pharmaceutical composition which comprises a mucopolysaccharides according to claim 29 in association with pharmaceutically acceptable vehicle.

⁶⁰
⁵⁹
61. Composition according to claim 60 in the form of a sterile injectable concentrated solution usable in therapeutics for the control of blood coagulation containing from 1,000 to 100,000 U (YIN-WESSLER) ml of said mucopolysaccharide, when these solutions are intended for sub-cutaneous injection, or containing again, from 500 to 10,000 u/ml of said mucopolysaccharide when it is intended for intravenous injection or for perfusion.

⁶¹
⁶². A composition according to claim 61 in the form of a sterile injectable concentrated solution useable in therapeutics for the control of blood coagulation containing 5,000 to 50,000 u/ml of mucopolysaccharides when intended for sub-cutaneous injection or 500 u/ml when intended for intravenous injection for perfusion.

⁶²
63. A method for the preventive treatment and/or the treatment of thrombosis comprising the use of a composition according to claim 60.

B

63
64. A mucopolysaccharide which comprises glucosamine units which has improved specific antithrombotic activity (as shown by inhibition of coagulation factor Xa), which mucopolysaccharide is free of hydroxyl groups on the primary carbon on the 6-position of the glucosamine units, the NMR analysis of which exhibits resonance signals in the region corresponding to chemical displacements of the order of 100 hpm (as shown by stars in Fig. 14), exhibits an additional resonance signal in the 60 ppm region (as shown by a star in Figs. 14 and 15), exhibits another resonance signal in the 75 ppm region (as shown by a star in Fig. 15) and which mucopolysaccharide comprises one N-acetyl glucosamine unit for two units of 2-O-sulfate iduronic acid and for two-N-sulfate-glucosamine units.

64
65. The mucopolysaccharide of claim *64* which has a molecular weight in the range of about 2,000 to about 50,000.

65
66. The mucopolysaccharide of claim *64* which has a ratio of Yin-Wessler and USP titer of at least 6.

66
67. The biological composition of claim *64* which comprises a biologically acceptable carrier and, in a biologically active amount, the mucopolysaccharide of claim *64*.

67
68. A therapeutic method for controlling thrombosis in a patient which comprises administering to the patient in an antithrombotic amount, the composition of claim *67* and controlling thrombosis by inhibiting coagulation factor Xa.